Clinical Pharmacology Review of BLA 97-0736

Date: December 11, 1997

Reviewer: Carol Braun Trapnell, M.D.

Sponsor: Hoffman LaRoche, Inc.
Nutley, NJ

Product: Human anti-TAC (HAT) (dacliximab, Zenapax®) for Intravenous Infusion

Product Class: Recombinant humanized IgG1 anti-Tac monoclonal antibody that acts as an interleukin-2 (IL-2) receptor antagonist

Proposed Indication: Prophylaxis of acute organ rejection in patients receiving renal transplants. Dacliximab will be administered concomitantly with an immunosuppressive regimen, including cyclosporine and corticosteroids

Proposed "Clinical Pharmacology" Section in the Sponsor's Draft Labeling

CLINICAL PHARMACOLOGY: *Mechanism of Action:* ZENAPAX contains dacliximab, a recombinant, humanized IgG1 anti–Tac antibody that functions as an interleukin–2 (IL–2) receptor antagonist. Dacliximab binds with high affinity to the alpha, or Tac, subunit of the high–affinity IL–2 receptor complex and inhibits IL–2 binding and biological activity. Dacliximab binding is highly specific for Tac, which is expressed on activated but not resting lymphocytes. Administration of ZENAPAX inhibits IL–2–mediated activation of lymphocytes, a critical pathway in the cellular immune response involved in allograft rejection. Dacliximab saturates the Tac receptor for approximately 120 days at the recommended dosage regimen. No significant changes to circulating lymphocyte numbers or cell phenotypes were observed by fluorescence–activated cell sorter analysis. Cytokine release syndrome was not observed following ZENAPAX administration.

Pharmacokinetics: In clinical trials.involving renal allograft patients treated with a 1 mg/kg IV dose of ZENAPAX every 14 days for a total of five doses, average peak serum concentration (mean ± SD) rose between the first dose (21 ± 14 µg/ml, N=82) and fifth dose (32 ± 22 µg/ml, N=72). The mean trough serum concentration before the fifth dose was 7.6 ± 4.0 µg/ml. In vitro and in vivo data suggest that serum levels of 5 to 10 µg/ml

are necessary for saturation of the Tac receptors to block the responses of activated T lymphocytes.

Population pharmacokinetic analysis of the data using a two–compartment open model gave the following values for a reference 45–year–old male Caucasian patient with a body weight of 80 kg and no proteinuria: systemic clearance = 15.1 mL/h, volume of central compartment = 2.49 L, volume of peripheral compartment = 3.43 L. Factors identified to contribute to individual variability in systemic clearance included total body weight (12 mL/h at 40 kg to 18 mL/h at 130 kg), age (12 mL/h at 20 years old to 17 mL/h at 70 years old), gender (8% decrease in systemic clearance in females), proteinuria (14% increase in systemic clearance in patients with proteinuria 1+), and race (21% decrease in systemic clearance in non–Caucasian, non–Black patients). The estimated inter-patient variability (percent coefficient of variation) in systemic clearance and central volume of distribution were 15% and 27%, respectively. The estimated terminal elimination half–life for the reference patient was 20 days (480 hours), equivalent to the terminal elimination half–life for human IgG (18 to 23 days). Bayesian estimates of terminal elimination half–life ranged from 270 to 919 hours for 123 patients included in the population analysis. The influence of body weight on systemic clearance supports the dosing of ZENAPAX on a milligram per kilogram (mg/kg) basis. This dose maintains drug exposure within 30% of the reference exposure for patients with a wide range of demographic characteristics. No dosage adjustments based on other identified covariates (age, gender, proteinuria, race) are required for renal allograft patients.

Clinical Studies Submitted in Support of the Above Labeling

The sponsor has submitted 8 studies which collected data in support of the information contained in the "Clinical Pharmacology" section of the proposed label. This review will focus on the data from the five studies carried out in renal transplant patients, which represents the patient population for whom dacliximab is being evaluated for licensure.

Protocol NO14392 was a Phase 1 study which assessed the pharmacokinetics of four different doses/dosing regimens of dacliximab. These data were analyzed separately. Protocols NO14393 and NO14874 were randomized, double-blind Phase 3 studies to evaluate the effect of the addition of IV dacliximab 1 mg/kg qow for 5 doses to standard three-drug and two-drug regimens, respectively. Sparse sampling techniques were used to assess dacliximab pharmacokinetics in subsets of these two Phase 3 studies. The sponsor chose to pool the data from these three studies and then used population pharmacokinetic techniques to analyze these data. Study NO15301 was a drug-drug

interaction study done as part of a larger trial to assess concomitant dacliximab and mycophenolate resulted in a pharmacokinetic interaction. Finally, the 5th study (NO15318) in renal transplant patients is to evaluate the pharmacokinetics of dacliximab in pediatric patients. This study is ongoing and no data have been submitted to date.

This review will first focus on the pharmacokinetic analyses from the Phase 1 study alone (NO14392), then move to a review of the overall population pharmacokinetic analyses from the three studies as described above. The drug interaction data will then be discussed.

PHARMACOKINETICS OF DACLIXIMAB

PROTOCOL NO14392: A PHASE 1 RANDOMIZED TRIAL OF HUMANIZED ANTI-TAC (———— FOR PREVENTION OF ACUTE ALLOGRAFT REJECTION IN RECIPIENTS OF FIRST RENAL TRANSPLANTS

Investigators: Dr. R. Kirkman, Brigham & Women's Hospital, Boston, MA
Dr. F. Vincenti, UCSF, San Francisco, CA

Summary of the Study:

This phase 1 study was a randomized, open–label, multiple–dose trial conducted at two centers in 16 patients receiving their first renal transplant. Patients received 0.5 or 1.0 mg/kg of HAT administered IV over 30 minutes once every week or once every other week for a total of five doses (study days 0, 7, 14, 21 and 28 for the qw cohorts and study days 0, 14, 28, 42 and 56 for the qow cohorts). The first dose was given immediately before the transplant (day 0). All patients had blood obtained for determination of dacliximab concentrations just before and 30 minutes after the completion of infusion for doses 1, 3 and 5 and on 2, 7, 14 and 28 days after the fifth infusion (study days 30, 35, 42 and 56 for the qw cohorts and 58, 63, 70 and 84 for the qow cohorts). In addition, patients receiving dacliximab qow had pre- and one-hour post-infusion blood obtained with the 2nd dacliximab dose. Serum levels of dacliximab were measured by ———————————— , using a specific sandwich enzyme-linked immunosorbent assay (EIA) with a limit of sensitivity of 25 ng/ml. The interassay coefficient of variation was 7.1% and the intra assay coefficient of variation was 8.3%. All patients received standard immunosuppressive therapy consisting of cyclosporine, prednisone, and azathioprine. Patients were followed for 3 months (84 days) from the day of transplant and were assessed at regular intervals for safety as well as followed for acute rejection or loss of their allograft.

Study doses were selected based on pharmacokinetic and pharmacodynamic data

obtained from a study of dacliximab in patients with steroid-resistant graft versus host disease. This single dose study found that the serum half-life averaged 87 hours (range 41-363 hours) and analysis of peripheral blood lymphocytes showed dacliximab binding to the IL-2 receptor for up to 28 days following the single doses of 0.5, 1.0 and 1.5 mg/kg.

Study Results:

Nineteen patients were enrolled in this study. Pertinent demographics for each study cohort are shown below:

	0.5 mg/ kg qw	1.0 mg/ kg qw	0.5 mg/ kg qow	1.0 mg/ kg qow
Sex (M/ F)	3/ 2	4/ 0	2/ 3	1/ 4
Median age, y	41	40	38	50
Age range, y	32– 57	32– 58	33– 63	37– 54
Donor: Cadaveric	0	1	4	1
Living related	5	3	1	4
Weight (kg) (mean, range)	81 (40-113)	85 (80-92)	72 (57-85)	73 (51-101)
Race				
White	4	4	4	1
Black	0	0	0	2
Other	1	0	1	2

All patients were receiving cyclosporine, azathioprine and prednisone at various doses, as well as other medications to treat their underlying medical conditions. Sixteen patients received all 5 doses of study drug and completed the 3 month study. The three patients who dropped out of the trial each received one dose of dacliximab but withdrew from the study due to complications with the renal transplant.

Summary of Pharmacokinetics:

A population approach was used to determine the pharmacokinetics of dacliximab. Data was analyzed using NONMEM version 4 and the PREDPP subroutines ADVAN3 and TRANS3. The pharmacokinetic model used was a two-compartment, open model with zero-order input and first-order elimination from the central compartment. The model parameters were Cl, Vd of the central compartment, VD at steady-state and intercompartmental clearance, Q. Models were specified to examine the influence of covariates on the model parameters. The factors examined included age, body weight, gender and body surface area. Bayesian estimates of the terminal elimination constant were obtained using the subroutines listed above. This value was subsequently used to determine the terminal elimination half-life and the accumulation of dacliximab with subsequent dosing. Finally, simulated serum concentration time profiles were generated for each treatment group in the study using the final population pharmacokinetic models.

Using the above, the following parameters were generated for the pharmacokinetics of dacliximab:

$T_{1/2\beta}$ = 273 hrs (range 244-354)
$Cl = 0.0118 \pm 0.0007 \cdot (weight/75)^{0.463 \pm 0.192}$
$Vd_c = 2.39 \pm 0.134$ L
$Vd_{ss} = 5.30 \pm 0.675$ L

Effect of Anti-Dacliximab Antibodies on Dacliximab Pharmacokinetics:

Blood was obtained for determination of anti-dacliximab antibodies at baseline and at specified times during study participation. Determinations were made regarding the ability of these antibodies to neutralize dacliximab. The sponsor reported that 7 patients in the study developed varying concentrations of anti-dacliximab antibodies during their study enrollment. Three of these patients had anti-dacliximab antibodies only at baseline. One patient (————) who developed neutralizing anti-dacliximab antibodies by day 14 post transplant had an acute rejection episode which began on day 7 of the study and required treatment with OKT3. The other 3 patients with anti-dacliximab antibodies did not have any apparent clinical sequelae from the development of these antibodies. The sponsor did not comment on effects of anti-dacliximab antibody formation on the pharmacokinetics of dacliximab.

Medical Officer's Comments on Results of Protocol NO14392

1. The population model developed to analyze the serum concentrations of dacliximab obtained in this study appears to be appropriate. The model that was used provides good correlation between the actual and predicted concentrations of dacliximab, thus, the pharmacokinetic parameters that were generated from the population model provide a good reflection of the clearance, volume of distribution and elimination rate constant/serum half-life of dacliximab in these patients.

2. Evaluation of the individual dacliximab concentration data reveals that the inter-patient variability in the peak dacliximab concentrations (those obtained one hour post infusion) was substantial. Data obtained on the same study days varied about 2-3 fold amongst the 4 study subjects per cohort. However, the data obtained at the "trough" times as well as the data obtained following the 5th and final dose of study drug do not show nearly this degree of inter-individual variability. The reasons for these differences are not clear. A random sampling of the times of blood sampling indicate that the blood obtained for determination of the peak concentrations was generally obtained 30 minutes after the completion of the infusion, as per the protocol.

3. Evaluation of the dacliximab pharmacokinetic parameters in the patients who developed anti-dacliximab antibodies reveals no change in the pharmacokinetics of dacliximab in these patients when compared to the values obtained for the other study subjects. Thus, it is reasonable to conclude that this clinical outcome was not due to changes in the dacliximab serum pharmacokinetics.

POOLED DATA FOR POPULATION PHARMACOKINETIC ANALYSIS OF HUMANIZED ANTI-TAC (HAT, Dacliximab) IN RENAL TRANSPLANT PATIENTS: PROTOCOLS NO14392, NO14393 AND NO14874

Below is a brief summary of these three studies with emphasis of the pharmacokinetic portions of each trial.

1. Protocol NO14392: See page 3 of this review for a summary of this study.

2. Protocol NO14393, A Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial of Humanized anti-Tac with Standard Three-Drug Immunosuppressive Therapy for Prevention of Acute Allograft Rejection in Recipients of First Cadaver Renal Transplants

   This was a Phase 3 study in which dacliximab 1 mg/kg IV given qow x 5 doses was added to a three drug regimen of cyclosporine, prednisone and azathioprine and compared in a double-blind, placebo-controlled manner to patients receiving cyclosporine, prednisone and azathioprine. Patients were evaluated at 6 months and 1 year for acute rejection and 3 years for long term graft survival; other clinical outcomes were also assessed at those times. The study was carried out in 17 Centers in the US, Canada and Sweden. Patients in this study were adult men and women undergoing their first renal transplantation with a cadaveric kidney. Patients were given dacliximab immediately before transplantation, then qow for 5 doses. Only the U.S. sites participated in the pharmacokinetic portion of this study. Blood for the determination of dacliximab serum concentrations were obtained just before and immediately after the infusion of the first and fifth doses (days 0 and 56), then on days 70 and 84 of the study. Determination of anti-dacliximab antibodies was also done at regular intervals during the first 84 days of this study. Assessments of clinical outcomes were made at 1 and 3 years after entry into the study.

3. Protocol NO14874, A Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial of Humanized anti-Tac with Standard Two-Drug Immunosuppressive Therapy for Prevention of Acute Allograft Rejection in Recipients of First Cadaver Renal Transplants

This was a Phase 3 study in which dacliximab 1 mg/kg IV given qow x 5 doses was added to a two drug regimen of cyclosporine and prednisone and compared in a double-blind, placebo-controlled manner to patients receiving cyclosporine, and prednisone. Patients were evaluated at 6 months and 1 year for acute rejection and 3 years for long term graft survival; other clinical outcomes were also assessed at those times. The study was carried out in 19 Centers in the Europe, Canada and Australia. Patients in this study were adult men and women undergoing their first renal transplantation with a cadaveric kidney. Patients were given dacliximab immediately before transplantation, then qow for 5 doses. Only two sites (one in Sweden and one in Canada) participated in the pharmacokinetic portion of this study. Blood for the determination of dacliximab serum concentrations were obtained just before and one hour after the infusion of the first and fifth doses (days 0 and 56), then on days 70 and 84 of the study. Determination of anti-dacliximab antibodies was also done at regular intervals during the first 84 days of this study. Assessments of clinical outcomes were made at 1 and 3 years after entry into the study.

Of note is that the analytic methods used to determine dacliximab concentrations were identical to what was described for study NO14392.

Study Results

Demographics

The population pharmacokinetic analysis included data from 123 patients The overall patient demographics of the patients from the three studies included in the population pharmacokinetic analyses are shown below.

	Protocol NO14392 (n=19)		Protocol NO14393 (n=91)		Protocol NO14874 (n=13)	
Variable	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Total Body Weight (kg)	77.3 (18.5)	40.2 - 112.9	77.1 (18.0)	42.5 - 126.5	81.8 (20.0)	53.0 - 133.0
Ideal Body Weight (kg)	63.5 (14.8)	34.0 - 82.0	64.7 (11.2)	39.0 - 85.0	67.0 (8.2)	53.0 - 80.0
Age (years)	44 (9)	32 - 63	47 (13)	18 - 70	43 (14)	20 - 62
Gender	10M / 9F		55M / 36F		10M / 3F	
Race						
Caucasian/Black/Other	13 / 2 / 4		57 / 22 / 12		13 / 0 / 0	

A total of 583 samples from 124 patients were available for inclusion in this analysis. Of these, 41 (7.6%) were not included in the analysis due to missing dose and/or sample time information, or because of apparent sample labeling errors. This included 17/147 (11.5%) from NO14392, 23/382 (6%) from NO14393 and 1/54 (2%) from

NO14874. These errors also removed one patient from the analysis (from study NO14393), as the excluded sample was the only assessment of dacliximab concentrations for that patient. Therefore, the total number of samples included in the population pharmacokinetic analysis was 542, with a mean of 4.4 samples/patient.

The population pharmacokinetic model used in this analysis consisted of 4 basic components:

1. Structural pharmacokinetic model component: describes the serum concentration versus time profiles of dacliximab and the pharmacokinetic parameters. A two-compartment, open model with zero-order input and first order elimination for the central compartment was used to model the time course of dacliximab serum concentrations.
2. Pharmacokinetic covariates: describes the influence of fixed effects on pharmacokinetic parameters. The fixed effects evaluated included total body weight, ideal body weight, body mass index, gender, age, race and urine protein. The covariate models used were defined to represent changes in the above parameters observed from a hypothetical "reference " patient. The sponsor chose this reference patient from the population in the data set with demographic factors equal to the average weight and age or most prevalent (gender, urine protein, race) demographics in the data set. Thus, for this analysis, the "reference patient" was defined as a 45 year old Caucasian male weighing 80 kg within 0 proteinuria.
3. The inter-individual error model: this describes the unexplained variability between individuals based on the influence of the fixed effects.
4. Residual error model component: this describes the underlying distribution of error in the measured pharmacokinetic variable generated by the differences between the model-predicted dacliximab concentrations and the observed dacliximab concentrations.

Prior to the analysis, the sponsor randomly selected a subset of subjects (n=20) to serve as a validation data set for the final population pharmacokinetic model. The demographics for the model development and validation data sets are shown below:

Variable	Model Development Data Set (n=103) Mean±SD (Range)	Validation Data Set (n=20) Mean±SD (Range)
Total Body Weight (kg)	77.2±18.0 (40.2-126.5)	80.2±19.7 (57.3-133.0)
Ideal Body Weight (kg)	64.7±11.4 (39.0-85.0)	64.9±11.9 (34.0-82.0)
Age (years)	46±12 (18-69)	46±13 (24-70)
Gender	61M/42F	14M/6F
Race (Caucasian/Black/Other)	69 / 20 / 14	14 / 4 / 2
Protocol	15 NO14392 77 NO14393 11 NO14874	4 NO14392 14 NO14393 2 NO14874

The sponsor developed the population pharmacokinetic model using the development data set and then used the data from the patients in the validation data set to confirm the findings of the population pharmacokinetic model.

The population model developed estimated that the pharmacokinetic parameters for the reference patient as mentioned above would be as follows:

Cl = 0.0151 L/h
AUC(mg*hr/L)
1st dose 3599
5th dose 5065
$t_{1/2\beta}$ = 480 hr

Covariate analyses were done on the pharmacokinetic parameters Cl, central Vd, peripheral VD, and inter-compartment clearance, Q. Covariates found to contribute to the inter-individual variability in Cl included total body weight, age, gender, urine protein and race. Covariates identified to contribute to the variability in the central CV included age, urine protein and race. None of the covariates contributed to the intersubject variability in intercompartmental clearance. Gender was found to contribute to the inter-individual variability in the peripheral Vd.

The clinical significance of these covariate influences was assessed by using the final population model to simulate pharmacokinetic parameter values for patient groups representative of the extremes of the covariate influences within this study population. The demographic combinations of each group were selected to be representative of actual patients observed in this study population. The sponsor argues that the best index of exposure to dacliximab is given by the estimates of the AUC for the first dose and the fifth dose, AUC_1 and AUC_5, respectively. These values were used instead of an AUC value at "steady state", given the slow systemic clearance (and long serum half-life) preclude reaching a "steady state" with the 5 dose regimen.

The results are shown below:

Patient Group	Patient Representation	AUC_1 (mg*h/L)	AUC_5 (mg*h/L)	$t_{1/2\beta}$ (hr)
I	reference patient	3599	5065	480
II	low Cl patient	3827 (+6%)	6232 (+23%)	409
III	high Cl patient	3131 (-13%)	4210 (-17%)	418
IV	low V1 patient	4325 (+20%)	6023 (+19%)	499
V	high V1 patient	2554 (-29%)	3961 (-22%)	475

Simulated dacliximab concentration-time profiles for each patient group relative to the reference patient group were then performed which showed that the variability in the dacliximab exposures were within a reasonable range and should not result in any clinical significance. Of note was that the minimum concentrations remained above the 5 mg/L target concentration for at least 70 days post-transplant in all patient groups.

Finally, the data set of the patients chosen for the validation group was used in the final population pharmacokinetic model. The results of these analyses were in good agreement with the original population pharmacokinetic assessment.

Formation of Dacliximab Antibodies

Ten of the 83 evaluable patients who received dacliximab in study NO14393 (12%) and 22 of the 125 evaluable patients who received dacliximab in study NO14874 (22%) developed antibodies detected to dacliximab. Pharmacokinetic data was available only for the patients in study NO14393; the dacliximab (mean ± SD) values are shown in the following table:

Study Day	Antibody-Positive Dacliximab Patients (mean ± SD)	Antibody-Negative Dacliximab Patients (mean ± SD)
Day 0 Peak	24.1 ± 20.8 (n=8)	20.6 ± 13.8 (n=73)
Day 56 Trough	8.7 ± 2.9 (n=8)	7.6 ± 4.1 (n=70)
Day 56 Peak	41.8 ± 25.3 (n=8)	30.7 ± 21.4 (n=65)
Day 70	7.8 ± 2.8 (n=8)	7.2 ± 3.6 (n=61)
Day 84	3.4 ± 1.7 (n=9)	3.5 ± 1.9 (n=67)

Two of these dacliximab patients with anti–dacliximab idiotypic antibody titers had rejection episodes (patient ——— on day 131, and patient——— on day 181), whereas 13 of the 73 antibody–negative dacliximab patients (17.8%) also had rejection episodes. The comparable percentages of rejection episodes in antibody–positive and antibody–negative dacliximab patients (20% vs 17.8%) suggests that the presence in serum of anti–dacliximab idiotypic antibodies neither preceded, nor correlated with, rejection episodes in the small number of patients studied. FACS analysis data for dacliximab binding to IL–2R receptors on peripheral blood lymphocyte for two other antibody–positive dacliximab patients (patients ——— and ———) indicate that the IL–2R receptors on the lymphocytes of these patients were saturated from 90 to 120 days post-transplant. Neither of these patients experienced rejection episodes during the first 6 months after transplantation. Furthermore, examination of serum sIL–2R values for antibody–positive patients in this study show that mean and median percent increases from baseline between day 14 and day 56 were approximately 200% to 400% which was similar to the overall mean and median percentage increases from baseline observed for the dacliximab–treated patient population as a whole.

In study NO14874, five of the 22 patients with antibodies to dacliximab developed rejection episodes at days 6, 9, 12, 19 and 83 post-transplant; this rejection rate for these patients was similar to the rejection rate seen in patients who received dacliximab who did not develop antibodies to dacliximab (23% vs 31 %, respectively).

Thus, the sponsor concluded from the data from these 2 studies that suggest that the development of antibodies to dacliximab affects neither dacliximab pharmacokinetics or its efficacy.

Reviewer's Comments

1. The population analyses performed on this data set appear to be well done. The covariate analyses revealed, as a whole, that the only clinical significant adjustment in dosing that needs to be considered is to dose dacliximab based on the patient's weight. The description of these analyses in the proposed label for this product could be simplified to reflect this conclusion (see below).
2. The whole issue of the clinical relevance of the formation of dacliximab antibodies is a very interesting one. In these studies based on a very small number of patients, the data suggest that these antibodies do not seem to effect either the clinical pharmacokinetics or the effectiveness of this product. However, more data will be needed to definitively confirm these early results. These data would be of particular interest if the sponsor plans to evaluate the use of dacliximab in a re-treatment setting.

DRUG INTERACTIONS STUDIES WITH DACLIXIMAB

Protocol NO15301: A Phase I/II Randomized Double-Blind Placebo-Controlled, Pharmacokinetic and Tolerability Study Comparing Zenapax® Plus Standard Immunosuppressive Therapy (CellCept® + Neooral® + steroids) to Standard Immunosuppressive Therapy in Patients Receiving a First Renal Allograft from non-HLA Identical Donors

Investigators: Ginny Bumgardner, M.D., Ph.D., Ohio State University
Robert Gaston, M.D., University of Alabama
Robert Kirkman, M.D., Brigham & Women's Hospital
Mark Pescovitz, M.D., Indiana University
Flavio Vincenti, M.D., UCSF

Summary of the Study:

This was a randomized, double blind, placebo controlled study to investigate the pharmacokinetics, safety and efficacy of adding dacliximab to a three-drug immunosuppressive therapy (mycophenolate mofetil, cyclosporine and steroids) for prevention of acute rejection in the first 6 months post-transplant in patients receiving their first renal allograft. The primary objectives were to evaluate the effect of dacliximab on mycophenolate mofetil pharmacokinetics, evaluate the effect of mycophenolate mofetil on the pharmacokinetics of dacliximab and to evaluate the tolerability of dacliximab when administered in combination with the standard three drug immunosuppressive regimen including mycophenolate mofetil. A secondary objective was to provide preliminary information on the effectiveness of dacliximab and mycophenolate mofetil when used in combination to prevent acute allograft rejection.

Patients enrolled into this study were men and women > 13 years of age receiving their first renal allograft from a cadaveric or a non-HLA identical living donor. Subjects could not receive azathioprine or tacrolimus and did not have any significant active infection. Eligible study patients were randomized in a 2:1 ration to receive either dacliximab 1 mg/kg qow x 5 doses or placebo administered up to 24 hours before transplant. Mycophenolate mofetil was administered as 1 g po q12 hours; cyclosporine was administered in accordance with the therapeutic practice at each study center, and prednisone or methylprednisolone was administered as instructed in the protocol using a descending sliding scale for the duration of the study.

Blood was obtained for mycophenolate mofetil pharmacokinetics on days 28 and 56 at times 0, 0.5, 1, 1.5, 2, 4, 6 and 8 hours post dose. Blood was taken just prior to and immediately after dacliximab/placebo infusion on study days 28 and 56 (doses 3 and 5), then at days 59, 64, 70, 84 and 100.

Plasma levels of dacliximab were measured by ——————————————— using a specific sandwich enzyme-linked immunosorbent assay (EIA) with a limit of sensitivity of 25 ng/ml. The interassay coefficient of variation was ranged from 4% to 9%. Plasma samples were assayed for mycophenolic acid (MPA) and its inactive glucuronide conjugate, MPAG, by ——————————————— via HPLC. The overall interassay coefficient of variation was 7.8% and 6.4% for MPA and MPAG, respectively. The limit of sensitivity of the MPA assay was 0.1 µg/ml. The limit of sensitivity for MPAG was 4.0 µg/ml. However, all MPAG calculations were converted to MPA equivalent units by multiplying the ratio of the molecular weights of MPA and MPAG). Thus, the sensitivity limit for MPAG in MPA equivalent units was 2.38 µg/ml.

The pharmacokinetic parameters calculated for MPA and MPAG were Cmax, Tmax and AUC0-8. Analyses were done using actual as well as log-transformed values for Cmax and AUC0-8. An analysis of variance (ANOVA) appropriate for a parallel study with two periods (two-way) was used to compare pharmacokinetic parameters for MPA and MPAG with and without dacliximab. The ANOVA model included terms for treatment, patient, period and treatment period. Statistical comparisons were performed using SAS JMP. Version 3.1.6.2. For both MPA and MPAG, ordinary confidence intervals (90% and 95%) for the difference in least squared means were calculated and expressed as a percentage (test relative to reference) for the bioavailability computed parameters AUC0-8, Cmax, and Tmax for untransformed data and for long-transformed AUC0-8 and log-transformed Cmax.

Dacliximab concentrations were summarized using descriptive statistics. The pharmacokinetic parameters calculated using a model-independent method were terminal elimination rate constant (β), $t_{1/2}$, AUC_{ss}, Cl and Vd.

Study Results:

Seventy-six (76) patients were enrolled into this study, 50 of whom were randomized to the dacliximab group and 26 of whom were randomized to placebo. All but one of the placebo patients received at least one dose of trial drug and was transplanted. A total of 22 patients in the placebo group and 40 in the HAT group received all five doses of trial drug; 13 patients were prematurely withdrawn and received less than five doses. All patients were to be followed for 6 months irrespective of whether they received the full five doses of trial drug. There were no differences in the incidences of graft rejection, survival or adverse events.

Of the 50 patients randomized to receive HAT, 40 had complete plasma concentration data and were evaluable for the pharmacokinetic analysis of serum HAT levels. Sixty–one of the 75 patients who received mycophenolate mofetil in addition to either HAT (N = 40) or placebo (N = 21) had complete plasma concentration data and were evaluable for the pharmacokinetic analysis of MPA and MPAG.

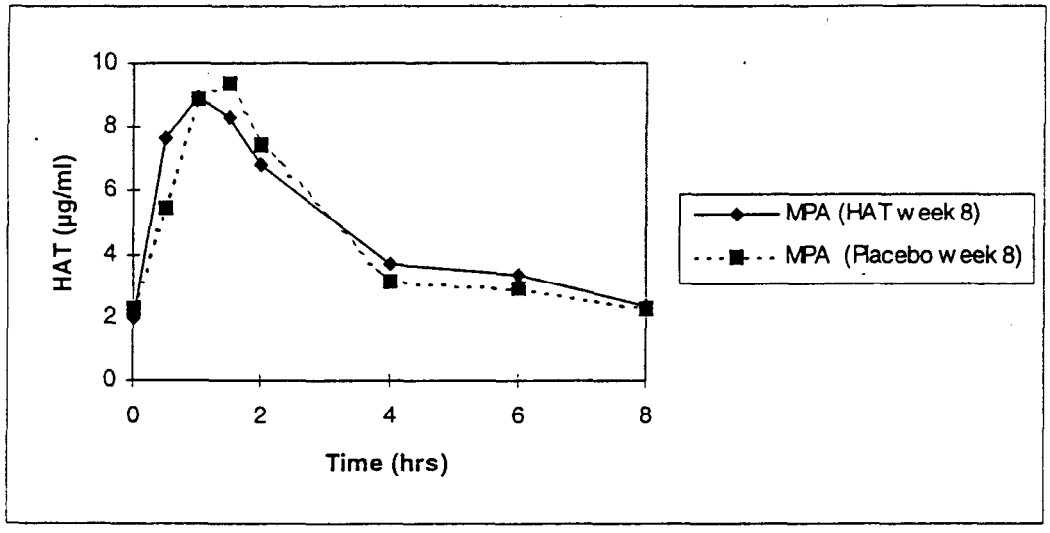
The demographic characteristics for the dacliximab and placebo groups were well matched. Of note, 28 males and 22 females received dacliximab; there were 17 and 8 males and females who received placebo.

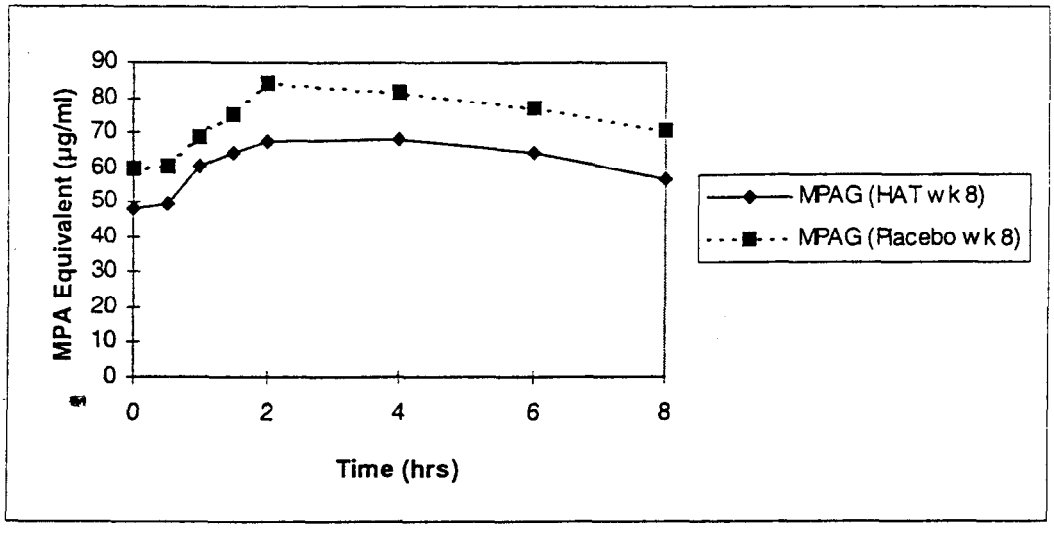
Pharmacokinetic Results:

Effects of Dacliximab on Mycophenolate mofetil Pharmacokinetics

A total of 40 patients (22 males and 18 females) randomized to receive HAT and 21 patients (15 males and 6 females) randomized to receive placebo had plasma MPA and MPAG concentrations available for analysis. Blood samples were obtained for analysis of these two mycophenolate mofetil analytes immediately before and for up to 8 hours post-dosing on study days 28 and 56.

The area-under the concentration-time curves for MPA and MPAG after 8 weeks of therapy (mean concentrations values) on either dacliximab or placebo are shown below; these results mirror what was seen at 4 weeks of therapy:





Quantitatively, the pharmacokinetic parameters (mean ± SD) determined from this study are as follows:

Parameter	Day 28 HAT (N = 40)	Day 28 Placebo (N = 21)	Day 56 HAT (N = 40)	Day 56 Placebo (N = 21)	ANOVA	90% CI
MPA						
C max (µg/mL)	10.8 (6.8)	10.6 (5.6)	12.8 (6.1)	11.6 (4.7)	NS	—
T max (h)	1.58 (1.22)	1.56 (1.53)	1.69 (1.69)	1.47 (0.81)	NS	NEQ (73.4, 142.3)
AUC 0– 8 (µg.h/ mL)	30.1 (13.3)	31.1 (12.4)	37.7 (18.2)	35.7 (14.0)	NS	—
Log– transformed C max	2.20 (0.63)	2.23 (0.53)	2.44 (0.48)	2.37 (0.43)	NS	EQ (83.3, 124.8)
Log– transformed AUC 0– 8	3.31 (0.44)	3.35 (0.44)	3.54 (0.43)	3.48 (0.47)	NS	EQ (83.4, 120.0)
MPAG (MPA Equivalent Units)						
C max (µg/ mL)	83.7 (33.9)	98.9 (30.3)	76.7 (22.5)	90.8 (31.5)	0.0377	—
T max (h)	3.80 (2.06)	3.79 (2.33)	3.94 (2.19)	3.72 (2.35)	NS	NEQ (82.9, 123.1)
AUC 0– 8 (µg.h/ mL)	554 (262)	673 (210)	495 (160)	609 (221)	0.0262	—
Log– transformed C max	4.36 (0.36)	4.55 (0.33)	4.30 (0.30)	4.45 (0.34)	0.0364	NEQ (73.9, 96.4)
Log– transformed AUC 0– 8	6.23 (0.41)	6.46 (0.33)	6.16 (0.30)	6.35 (0.35)	0.0160	NEQ (69.9, 93.2)

Note: CI = confidence interval, EQ = equivalent, HAT = humanized anti–TAC, NEQ = not equivalent, NS = difference between means is not statistically significant ($p > 0.05$).
ANOVA results reported for treatment effect.
90% confidence interval results based on log–transformed C_{max} and AUC_{0-8} and on untransformed T_{max} data. The two groups were considered equivalent if the 90% confidence interval was within 80 to 125% limits of the range for log transformed data, or within 80% to 120% limits of the range for untransformed data, specified for bioequivalence.

The sponsor concluded the following from the above data:

1. The pharmacokinetics of mycophenolate (MPA) were unchanged in the presence of dacliximab.
2. There were changes seen in the pharmacokinetics of the glucuronide metabolite, MPAG. Lower mean Cmax and AUC0-8 hour values for MPAG were seen when compared to the placebo group. These changes were statistically significant using an ANOVA as indicated in the above table. The reason for this difference was not obvious; the sponsor hypothesized that this might be due to the slightly better renal function that occurred in patients who received dacliximab.

Effects of Mycophenolate Mofetil on the Pharmacokinetics of Dacliximab

A total of 40 patients (22 males, 18 females) had serum dacliximab concentrations obtained for purposes of analysis. The parameters obtained from these data were then compared to the pharmacokinetic parameters obtained for dacliximab in Study NO14393. (This study was described earlier in this review, was a Phase 1 study of

dacliximab was added to a triple-drug regimen of cyclosporine, steroids and azathioprine.) Comparisons of these data is shown in the below.

Parameter	Protocol	Mean	SD	Median	Range Min	Max	N
t½ (h)	NO15031 (w/ MMF)	401.5	—	421.5	156.6	2167.3	28
	NO14393 (w/ o MMF)	412.3[a]	—	446.6	281.1	923.2	91
AUC ss (mg·hr/L)	NO15301 (w/ MMF)	4582.2	2623	4033.5	373.2	9578.9	25
	NO14393 (w/ o MMF)	5208.2	1014	5053.5	3040.5	7984.0	91
CL (L/ h)	NO15301 (w/ MMF)	0.029	0.038	0.016	0.007	0.182	25
		0.016	0.006[b]				21
	NO14393 (w/ o MMF)	0.015	0.003	0.015	0.008	0.024	91
Vd (L)	NO15301 (w/ MMF)	35.7	111.9	9.2	2.9	569.7	25
		10.2	5.4[b]				21
	NO14393 (w/ o MMF)	9.3	3.1	9.6	4.9	17.3	91

[a]Arithmetic mean of Bayesian estimates from population pharmacokinetic analysis.
[b]Excluding values of four patients in whom estimation of pharmacokinetic parameters appeared to be in error because of the pharmacokinetic methodology employed in the derivation of AUCss .

Of note is that 4 patients were excluded from a subanalyses of these data due to clearance values that was 3- to 12- fold higher than the median value for the study population. The sponsor believe that these high estimates were perhaps due to the methodology that had been used in the calculation of the AUCss for these patients.

The Effect of Dacliximab on the Pharmacokinetics of Cyclosporine

No formal pharmacokinetic study was done to assess pharmacokinetic effects of these two drugs. However, the sponsor did assess trough cyclosporine concentrations as well as mean doses of cyclosporine for the first 3 months of the trial in the patients who received both dacliximab and placebo in both of the pivotal clinical trials (NO14393 and NO14874). NO14393 evaluated dacliximab when added to a triple drug regimen of cyclosporine, steroids and azathioprine whereas NO14874 evaluated dacliximab when added to a two drug regimen of cyclosporine and steroids. The sponsor concluded from these data that dacliximab had no appreciable effect on the pharmacokinetics of cyclosporine.

These results are shown in the next two tables:

Comparison of Mean (±SE) Daily Dose of Cyclosporine (mg/kg) between Patients Receiving Dacliximab and Patients Receiving Placebo during the First 3 Months Post-transplant in Clinical Efficacy Trials

	Protocol NO14393		Protocol NO14874	
Study Day	Placebo (n= 114– 126)	Dacliximab 1 mg/ kg qow (n= 113– 122)	Placebo (n= 109– 129)	Dacliximab 1 mg/ kg qow (n= 120– 135)
7	8.39 (0.28)	8.83 (0.29)	7.40 (0.24)	7.63 (0.25)
28 (1 month)	7.41 (0.29)	7.90 (0.32)	5.63 (0.24)	5.65 (0.22)
84 (3 months)	5.75 (0.25)	6.18 (0.30)	4.46 (0.18)	4.57 (0.17)

Comparison of Mean (± SE) Trough Cyclosporine Concentrations (ng/mL) between Patients Receiving Dacliximab and Patients Receiving Placebo during the First 3 Months Post-transplant in Clinical Efficacy Trials

	Protocol NO14393		Protocol NO14874	
Study Day	Placebo (n= 100– 118)	Dacliximab 1 mg/ kg qow (n= 108– 119)	Placebo (n= 105– 123)	Dacliximab 1 mg/ kg qow (N= 114– 129)
7	276 (15)	297 (16)	353 (21)	315 (13)
14	303 (16)	300 (13)	311 (16)	324 (17)
28 (1 month)	335 (16)	354 (23)	281 (15)	328 (22)
84 (3 months)	269 (12)	295 (18)	286 (25)	282 (21)

Reviewer's Comments on Dacliximab Drug Interaction Data

It is important to note that the clinical pharmacology properties of dacliximab lends itself to a low level of suspicion to the possibility of pharmacokinetic drug interactions with respect to enzymatic inhibition/enhancement, protein binding, competing routes of elimination or effects on gastrointestinal absorption. Competition for binding onto to IL-2 receptor is the most likely mechanism for dacliximab drug interaction. However, since this mechanism of action is unique among the drugs currently used for prevention of organ rejection, thus it is again highly unlikely that IL-2 binding site competition would account for any drug interactions.

The addition of dacliximab to the two immunosuppressive regimens used in the above-mentioned studies added a therapeutic agent whose mechanism of action and clinical pharmacologic properties differed from the other agents being used. The hypothesis being tested was that this new agent, with its unique properties, would add to the pharmacodynamic effect of the regimen, measured by the incidence of organ transplant rejection. This beneficial pharmacodynamic effect is the goal of adding dacliximab to the current regimen to prevent organ rejection and was, in fact, what was observed with the pivotal clinical trials submitted in this application.

The sponsor performed a formal study to assess a pharmacokinetic interaction between mycophenolate mofetil and dacliximab. The study was designed to assess these interactions using parallel groups, one which received dacliximab while the other received placebo. The data from this trial suggest no differences in the mycophenolate pharmacokinetics with a curious difference in the pharmacokinetics of the glucuronide metabolite, MPAG. The sponsor hypothesized that the lower MPAG concentrations in the dacliximab group could be related to slightly better renal function, causing a greater excretion of this salt. However, there is no urine concentration data available to confirm this hypothesis. It is also possible that the differences seen are due to the expected inter-individual variability in mycophenolate mofetil pharmacokinetics. However, whatever the mechanism, there is little clinical relevance to this finding, given that MPAG is an inactive metabolite if mycophenolate mofetil. Finally, the use of "historical controls" for a comparison of the dacliximab pharmacokinetics when given with mycophenolate is acceptable given the patient population and, again, the fact that the suspicion for a pharmacokinetic interaction between these two therapeutic agents is low.

The assessment of a cyclosporine-dacliximab pharmacokinetic interaction was done using more of a screening technique as opposed to a formal, clinical pharmacokinetic study. This was an acceptable approach, again, because the likelihood of this interaction is so low given the clinical pharmacology of these compounds. These data suggest that there is no effect of dacliximab on cyclosporine pharmacokinetics. The usual clinical practice is for cyclosporine levels to be regularly monitored with appropriate dosage adjustments when needed. Thus, it seems appropriate to conclude that dacliximab most likely has no pharmacokinetic effect on cyclosporine.

Reviewer's Comments on the Proposed Label

The sponsor is proposing a very detailed description of the population pharmacokinetic analysis to describe the pharmacokinetics of dacliximab. It is preferable to make this section more readable by replacing the proposed information with fewer summary sentences, the focus of which is that the data were analyzed using the covariates as described, and only weight was found to be of significant enough to warrant dose adjustment. Suggested wording for this section is below:

> Population pharmacokinetic analysis of the data using a two-compartment open model gave the following values for a reference patient (45-year-old male Caucasian patient with a body weight of 80 kg and no proteinuria): systemic clearance = 15 mL/h, volume of central compartment = 2.5 L, volume of peripheral compartment = 3.4 L. The estimated terminal elimination half-life for the reference patient was 20 days (480 hours), which is similar to the terminal elimination half-life for human IgG (18 to

23 days). Bayesian estimates of terminal elimination half-life ranged from 270 to 919 hours for the 123 patients included in the population analysis. The influence of body weight on systemic clearance supports the dosing of ZENAPAX on a milligram per kilogram (mg/kg) basis. This maintained drug exposure for patients studied to be within 30% of the reference exposure. Covariate analyses showed that no dosage adjustments based on age, race, gender, or degree of proteinuria, are required for renal allograft patients. The estimated inter-patient variability (percent coefficient of variation) in systemic clearance and central volume of distribution were 15% and 27%, respectively.

CONCLUSIONS

1. Through the use of population pharmacokinetics, the sponsor has adequately defined the clinical pharmacokinetics of daclizimab in patients receiving their first renal transplant. Further, the use of covariate analyses demonstrated that adjusting the dose solely on patient's body weight was the only clinically relevant factor to adjust dose when considering the effects of all of the examined covariates as a whole.

2. It is reasonable to conclude that daclizimab does not affect the pharmacokinetics of mycophenolate mofetil, its glucuronide salt or cyclosporine based on the clinical pharmacology of daclizimab and the data presented in this application.

3. The "Clinical Pharmacology" section of the label should be simplified as suggested above.

4. Further assessment of the possible effect of daclizimab antibody formation on the pharmacokinetics and pharmacodynamics of daclizimab should be suggested to the sponsor as part of their Phase 4 efforts.

CONCLUSIONS - continued

5.

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